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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/642,492	08/18/2000	Gary Van Nest	377882000800	7136

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EXAMINER	
FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/642,492	VAN NEST ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11,13-23,25-33,37-42 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 11, 13-23, 25-33, 37-42 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In paper no. 15, applicant cancelled claims 4-6 and amended claims 1, 37, 40 and 53. Claims 1, 11, 13-23, 25-33 and 37-53 are pending. Claims 43-52 are withdrawn from consideration due to a non-elected invention. Claims 1, 11, 13-23, 25-33, 37-42 and 53 are under consideration. Upon further search and consideration, new grounds of rejection are required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 13-23, 25-33, 42 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for modulating a Th-1 immune response by increasing an IgG2a response and decreasing an IgG1 response against a second antigen by co-administering the second antigen with an ISS-antigen complex, does not reasonably provide enablement for modulating a Th-1 response to a second antigen that is co-administered with the ISS-antigen complex at a different site of administration from the ISS-antigen complex. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. (In the previous rejection, it is noted that claim 42 was inadvertently omitted from the rejection and is included here.)

Applicant is convincing that the instant claims are drawn to co-administration of the ISS-antigen conjugate and the secondary antigen, that is, administering the antigens sufficiently close

in time that an immune response is modulated. Applicant also pointed to simultaneous administration in the disclosure.

With respect to the lack of enablement for generating an immune response when the complex and the second antigen are administered at different sites, applicant disagrees. Applicant asserts that a Th1 response is induced and points to Table 6. Applicant states that there is a 4-fold increase in the anti-βgal IgG2a response compared to the response induced by βgal alone.

Applicant's arguments have been fully considered, but are found unpersuasive. On page 56, lines 3-15, the disclosure summarizes the results of the ISS-antigen and βgal administration at different sites. In lines 3-4, the specification states, "delivery of AIC at a distant site had little effect on anti-βgal IgG2a responses." Same day injection at distant sites resulted in only a 2.3 and 1.4-fold increase in anti-βgal IgG2a responses for each respective injection using 1μg AIC and only a 2.8 and 4-fold increase in anti-βgal IgG2a responses for each respective injection using 10μg AIC. On page 56, lines 10-11 and 14-15, the disclosure specifically states, "AIC at either dose had little effect (three fold or less) on anti- βgal IgG1 responses...delivery of AIC to a site distant from the unrelated antigen had little effect on the Th1 response to that antigen." Therefore, due to the direct teachings in the disclosure, it is maintained that the claims are not enabled for modulating an immune response to a second antigen when the ISS-antigen conjugate is administered at a distant site. It is maintained that an undue quantity of experimentation would be required of the skilled artisan to use the invention commensurate in scope with the instant claims.

Claims 1, 11, 13-23, 25-30, 32, 33, 37-42 and 53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using an ISS molecule comprising SEQ ID NO: 1, does not reasonably provide enablement for IS sequences that are shorter or do not conform to the enabled motif. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This is new grounds of rejection.

The claims are drawn to a method of modulating an immune response to a second antigen by co-administering an immunostimulatory sequence (ISS) conjugated to a first antigen and a second antigen. The ISS comprises 5'-cytosine, guanine-3', 5'-TCG-3' or the sequences recited in claims 26-30. Although claims 37-41, are drawn to a composition comprising the components used in the method, the claims require that the ISS be immunostimulatory. As evidenced by the teachings of Fearon et al., a polynucleotide merely containing the short sequences recited are not immunostimulatory. That is the basis of this enablement rejection.

Fearon et al. (European Journal of Immunology. 2003; 33: 2114-2122) teach minimal length requirements for ISS molecules to induce an immune response, see the discussion section. Fearon et al. specifically teach that while "ACGTTCG" contains two CpG sequences, it lacks activity in human PBMC's, see section 2.2 and figures 1 and 2. The "ACGTTCG" sequence of Fearon et al. is one residue shorter than the second sequence recited in claim 30. Since Fearon et al. were unable to generate a sufficient immune response with "ACGTTCG" and the disclosure does not teach inducing an immune response with any sequence other than SEQ ID NO: 1 in the working examples, the skilled artisan would not predict that the shorter sequences claimed would generate an effective immune response. Fearon et al. also teach that a consensus ISS motif has

been recognized in murine models, the equivalent human motif has yet to be identified, see the first paragraph of the discussion section. The disclosure does not identify a human immunostimulatory ISS motif comprising the minimum nucleotide sequences recited in the claims. The working examples only induce an immune response using SEQ ID NO: 1. The specification does not provide any guidance to the skilled artisan for how to make the instant sequences sufficiently immunogenic or how to use sequences, such as AACGTTCG recited in claim 30, that are not immunogenic. Therefore, it is determined that the claims would require undue experimentation to make and use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (WO 98/55495, "Schwartz") **or** Carson et al. (WO 98/16247, "Carson"), as further evidenced by Horner et al. (Cellular Immunology. November, 1998; 190: 77-82) or Chu et al. (Journal of Experimental Medicine. 1997; 186 (10): 1623-1631).

The sequences required by claims 1, 11, 13-23, 25-30, 32, 33, 37-42 and 53 are required to possess certain nucleotides and be immunostimulatory. The basis of rejection of these claims under 35 USC § 103 are polynucleotides that comprise the structural limitations recited and possess the functional characteristic of being immunostimulatory, i.e. SEQ ID NO: 1. SEQ ID NO: 2 of Schwartz is identical to SEQ ID NO: 1 instantly claimed. Carson also teaches SEQ ID

NO: 1 instantly claimed, see the Geneseq database. Accession no: V32079. April 23, 1998, seqeunce alignment provided in Office action mailed 7/30/02.

Applicant argues that there is no suggestion in either Carson or Schwartz to modulate an immune response, i.e. a Th1 response, to a second antigen upon administration of an ISS-antigen conjugate. Applicant asserts that the citation on page 5 of Schwartz does not imply that there is more than one antigen present. Applicant argues that Schwartz does not provide an example of ISS administered with multiple antigens.

Applicant's arguments and a review of the reference have been fully considered, but are found unpersuasive. While lines 1-2 on page 5 of Schwartz may be ambiguous with regard to the components, page 12, lines 9-15 are not. Schwartz specifically suggests administering ISS "in conjunction with *one or more* members of the group of immunomodulatory molecules comprising *antigens*" (emphasis added), see page 12, lines 9-10. On page 12, lines 29-31, Schwartz states that "[t]he ISS and the antigen...can be administered together in the form of a conjugate or co-administered in an admixture sufficiently close in time so as to modulate an immune response." This teaching encompasses co-administration of an ISS-antigen conjugate co-administered with another antigen(s). While Schwartz does not provide a working example administering an ISS-antigen and a second antigen, teachings within the reference certainly suggest this concept. Schwartz teaches that ISS molecules induce a Th1 immune response (see page 3, lines 32-35) and specifically teach administering ISS-antigen conjugates as well as ISS/antigen mixtures, see claims 25-27 for example. Therefore, it is maintained that administering a second antigen with an ISS-antigen conjugate would have been prima facie

obvious to one of ordinary skill in the art at the time the invention was made in view of Schwartz, absent unexpected results to the contrary.

With respect to the teachings of Carson, applicant argues that the examiner has not pointed to a teaching or suggestion within Carson to co-administer a second antigen with the ISS-antigen conjugate.

In response to applicant's argument that there is no suggestion to combine a second antigen in the teachings of Carson, it is noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art (emphasis added). See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In the immunization art, ordinary artisans routinely administer multiple antigens to induce an immune response to different portions of a agent. Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have been motivated to administer a second antigen in order to elicit a specific immune response against another portion of a pathogen or another strain of virus. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Carson teaches that antigens administered with an ISS conjugate elicit a Th1 immune response. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent evidence to the contrary.

Applicant further argues that Carson teaches away from the instant invention because the reference teaches that an un-conjugated antigen is processed differently than a conjugated antigen.

Applicant's arguments have been fully considered, but are found unpersuasive. Although Carson speculates that antigens may be processed differently in the citation referred to by applicant, Th1 immunopotentiation is observed with an ISS-antigen conjugate and an ISS antigen mixture, see Figure 1. Therefore, administering an ISS-conjugate and a second, un-complexed antigen would have been prima facie obvious from the teachings of Carson. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing a Th-1 response against a second antigen that is administered with an ISS-antigen complex because Carson teaches that ISS induces a Th-1 response against antigens that are administered with the ISS molecule, see Figure 1 and claims 54 and 66.

Applicant also argues that there is no suggestion or motivation to modify the teachings of Carson or Schwartz and neither reference provides a reasonable expectation of success to practice the invention. Applicant further argues that the expected immune response generated against a second antigen co-administered with ISS is not the same as that obtained with an ISS-antigen conjugate. Applicant points to Dr. Van Nest's declaration, unexpectedly showing a higher Th1 response to a second antigen when co-administered with an ISS-antigen conjugate.

Applicant's arguments have been fully considered, but are found unpersuasive. Carson or Schwartz, respectively, teach modulating a Th1 response to an un-complexed antigen upon co-administration of an ISS molecule, see the previous citations. The instant claims are drawn to modulating an immune response to a second antigen. The claims further require that the immune

response to the second antigen is a Th1 response. As demonstrated by the teachings of Carson (Figure 1), Horner et al. (see Figures 1 and 2) or Chu et al. (results and discussion sections), un-conjugated antigens co-administered with ISS, induce a Th1 response against the antigens. Schwartz teaches or Carson suggests administering an ISS-antigen conjugate and ISS antigen mixtures along with multiple antigens. Therefore, administering multiple antigens with the ISS conjugate would have been prima facie obvious in view of the teachings of Carson or Schwartz. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for inducing a Th1 response against an un-conjugated antigen that is co-administered with an ISS molecule-antigen conjugate because Carson, Horner et al. or Chu et al. specifically teach inducing a specific Th1 response to an antigen that is co-administered with an ISS molecule. Therefore, the addition of a second antigen is either explicitly suggested (Carson or Schwartz) and the Th1 response induced against an antigen co-administered with an ISS molecule is taught in the art, see Carson, Horner et al. or Chu et al. These facts would have rendered the instant claims prima facie obvious to one of ordinary skill in the art at the time the invention was made as no unexpected results have been demonstrated in the specification or the declaration. Therefore, it is maintained that the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claim 15 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Lee et al. (Ann Med. 1998; 30: 460-468).

Applicant argues that Lee does not supply what is missing from the primary references. Applicant further submits that there is no suggestion to modify the references to arrive at the claimed invention.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been obvious from the teachings of Schwartz or Carson, respectively, as evidenced by Horner et al. or Chu et al. Each reference individually teaches inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, Lee is only required to teach a limitation that is not taught by the primary references.

Lee et al. teach that the influenza nucleocapsid protein is the least effected by antibody-induced antigenic drift and studies using DNA encoding this protein have demonstrated protection, see "infectious diseases" on page 465. One of ordinary skill in the art would have been motivated to incorporate a protein into a treatment composition that has already demonstrated protective properties in other studies. Furthermore, one of ordinary skill in the art would have had a reasonable expectation in producing the claimed invention because Schwartz or Carson teach compositions and methods comprising ISS and proteins that modulate the immune response and Lee et al. also teach subsequent Th1 responses upon administration of ISS with DNA encoded antigens, see "mechanism of action..." on pages 463-464. Therefore, the invention as a whole is prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Claims 16 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al., as further evidenced by Horner et al. or Chu et al., as applied to

claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Durali et al. (J of Virol. 1998; 72(5): 3547-3553).

Applicant also argues that this reference does not overcome the deficiencies of Carson or Schwartz or provide motivation to arrive at the claimed invention.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been obvious from the teachings of Schwartz or Carson, as further evidenced by Horner et al. or Chu et al. Each reference individually teaches inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, Durali et al. is only required to teach a limitation that is not taught by the primary references.

Durali et al. teach that the gag protein is capable of cross-reactivity in different patients infected with different clades of HIV, see the abstract. Since high variability in HIV is a major obstacle in selecting an antigen for a vaccine candidate and Durali et al. have been able to identify a conserved protein, one of ordinary skill in the art would be motivated to incorporate this protein into a composition to induce an immune response against the antigen. Furthermore, the skilled artisan would have a reasonable expectation in producing the claimed invention because Schwartz et al. or Carson et al. teach that the protein portion of the composition and method could be a wide variety of proteins from viruses.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. or Carson et al., as further evidenced by Horner et al. or Chu et al., as applied to claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 above, and further in view of Anderson (US Patent 4,673,574).

Applicant argues that none of the references alone or in combination teach potentiating an immune response against a second antigen that is co-administered with an ISS-antigen complex.

Applicant's arguments have been fully considered, but are found unpersuasive because administering a second antigen with an ISS-antigen conjugate would have been prima facie obvious from the teachings of Schwartz or Carson, as further evidenced by Horner et al. or Chu et al. Each reference individually teaches inducing a Th-1 response against an antigen present in a mixture with an ISS molecule or with an ISS-antigen complex. Therefore, is Anderson is only required to teach a limitation that is not taught by the primary references.

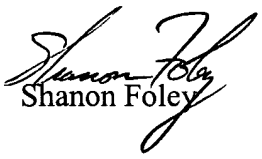
In the instant case, one of ordinary skill in the art at the time the invention was made would have been motivated to use the diphtheria components taught by Anderson in the method and composition taught by taught by Schwartz et al. or Carson et al. when administering the composition to children or immunocompromised individuals because the diphtheria toxins aid in eliciting a protective immune response, have no toxicity, and can be administered safely to children, see column 5, lines 10-19 and column 14, table 7. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation in producing the claimed invention because Schwartz et al. or Carson et al. teach that the ISS/antigen composition can be combined with any known vaccine component and the diphtheria toxins taught by Anderson are well known.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Shanon Foley